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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,914	05/30/2001	Neil Andrew Williams	5440US.cip	8062

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EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/867,914	Applicant(s) Williams et al
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 20, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above, claim(s) *1-9 and 13-46* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Claims

1. The Examiner acknowledges response to restriction requirement. Applicant elected, with traverse, Group II, claims 10-12. Applicant argues that the claimed subject matter has been already examined in the parent application 08/999458 which matured into US Patent 6,287,563. However, the claims under examination in the parent case were drawn to a particular method of use, rather than pharmaceutical composition elected in the instant application. Further, Group II is the technical feature that links Groups I-V. Group II is not the contribution over the prior art because it is suggested by prior art discussed in the art rejections below. The restriction requirement is still deemed proper and is therefore made FINAL. Claims 1-9,13-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups. Cancellation of claims 1-9,13-46 is requested.

Claim Objections

2. Use of abbreviation GM-1 (claim 1 referred to in claim 10) is noted. For clarity "ganglioside GM-1" is suggested to be used at the first appearance of the abbreviated term.

Claim Rejections - 35 U.S.C. § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

A. Claim 10 addresses agent which is not identified in the claim, but is rather recited in claim 1 which is not under consideration. Please incorporate definition of the agent into claim 10. The remaining rejections in this section assume that such incorporation has been made.

B. It is not clear, whether the term "agent" used in claims 10 means a single compound or a composition.

C. The term "GM-1 associated activity" in claims 10 is a relative term which renders the claim indefinite. It is not clear what kind of "associated activity" is encompassed by the claim. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "associated activity activity". Is it activity directly regulated by GM-1, or activity regulated by

other signaling events which are indirectly affected by GM-1? Accordingly, it is not possible to determine what agents are embraced within the scope of the claims.

D. It is not clear whether the term "modulation" in regard to GM-1 activity means activation or inhibition or both.

E. As claim 10 incorporates the definition of the agent from claim 1, the amount of the agent is not quite clear. Is the agent in the composition is in the amount that specific for the treatment of diabetes?

Claim Rejections - 35 U.S.C. § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Ctx and Etx and their B subunits, does not reasonably provide enablement for agents, other than Ctx and Etx or their B subunits, and having GM-1 binding activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The breadth of the claims encompasses any agent capable of modulating activity associated, in any way, with GM-1 activity.

Possible role of interaction of certain pharmaceuticals with GM-1 only recently have become known as a mechanism of their action. For example it has been demonstrated that the immunosuppressant, cholera toxin B subunit, interacts with GM-1. See Francis, abstract. However, there is no guidance in the prior art on the type and structure of compounds which would render them capable of binding to GM-1 or modulating activity of events, directly or indirectly related to GM-1. Rather, it is clear that capability for an interaction with GM-1 is sensitive to the structure of the ligand. The example of B chain of cholera toxin is illustrative on the unpredictability in the art: Sandkvist has shown that even a slight change in the structure of the B subunit of cholera toxin reduces its ability to bind to GM-1. See Sandkvist, abstract, lines 6-8. Therefore, there is a lack of predictability in the prior art.

The instant disclosure describes use of B-chain of enterotoxin and its mutants. There are no working examples of making and/or using of any agents. Although there is a mention on the possibility of the use of monoclonal antibodies (p. 12, second paragraph), there is no guidance on how to select and prepare any other agents which have binding activity to GM-1 and are other than Ctx and Etx or their B subunits. As the claims are drawn to agents which can "modulate GM-1 associated activity, it

encompasses numerous products, e.g., products which may be able to bind to GM-1 in test conditions (such as metal ions in solution, various sorbents, etc) but may not be effective as pharmaceuticals. There is no guidance in the specification on how to select operative embodiments out of plethora of possible agents. Further, even for agents capable of binding to GM-1 receptor *in vivo* there is no guidance on whether an agent should be selected from those that trigger events mediated by GM-1 receptor, inhibit them, or simply bind to GM-1 without any physiological consequence. Therefore, one skilled in the art would not be able to make the invention as claimed because selection of agents suitable for the claimed method of treatment would require undue experimentation.

Next, there is no guidance in the specification on how to use agents which modulate GM-1 associated activity, and are not B chains of Ctx and Etx. There is no guidance on dosage ranges for agents other than B chains of Ctx and Etx, nor there are any guidelines for determination of these dosage ranges. Combined with the lack of guidance of how to select agents other than B chains of Ctx and Etx, and how to select their dosages, the use of such potential candidate compounds will require additional undue experimentation.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art

one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Claim Rejections - 35 U.S.C. § 102 and 103.

5. Claims 10-12 is rejected under 35 U.S.C. 102(b) as anticipated by Yankelevich (J. Immunology, 154, 3611-3617, 05/95), as evidenced by Francis.

The instant claims are drawn to agents capable of modulating GM-1 associated activity. GM-1 is a glycosphingolipid ganglioside. Note that it is known in the prior art that cholera toxin B chain (Ctx-B) binds to GM-1 (see, e.g., Francis, abstract).

Yankelevich teaches composition comprising B subunit of Ctx and its use for improvement of T cell immune responsiveness and treatment or prevention of graft-versus-host disease. Treatment with Ctx-B composition resulted in improvement of T cell responsiveness, decrease in accumulation of CD8-positive T cells in spleen, and improvement in humoral immunity. Pretreatment of inocula with B subunit of Ctx impaired the ability of C57Bl/6 T cells to induce acute GVHD. See abstract. See p. 3616, first paragraph. Ctx-B was used in an aqueous solution which is pharmaceutically acceptable.

Therefore, the prior art composition comprising B subunit of Ctx anticipates the instantly claimed composition comprising agent capable of modulating GM-1 associated activity.

In regard to claims 11,12, reciting intended use, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. *In re Pearson*, 494 F.2d 1399, 181 USPQ 641 (CCPA 1974). Suggested use limitations do not impart patentability to composition claims where the composition is otherwise anticipated by the prior art.

6. Claims 10-12 are rejected under 35 U.S.C. 102(a) as anticipated by Holmgren et al. (WO 95/10301; 04/20/95) in view of Francis and Kaper.

The instant claims are drawn to method of treatment of an autoimmune disease by an agent having GM-1 binding activity. GM-1 is a glycosphingolipid ganglioside.

Holmgren

Holmgren teaches treatment of various autoimmune disorders by immunological tolerance-inducing agent comprising a mucosa-binding molecule linked to a specific tolerogen. (See claims 1,9,16). Mucosa-binding molecule can be derived from mucosa-binding structures of bacterial toxins, bacterial fimbriae, viral attachment

proteins and plant lectins. See claims 1-5, Table 1(pp. 9-10). Tolerogen can be selected from various antigens. See claims 6, 10 and p. 13. In particular, mucosa-binding molecule is B subunit of cholera toxin or enterotoxin (see claim 5). The agents of the references are administered in a form of pharmaceutical composition (Examples 6-8). The tolerance-inducing agents of Holmgren will inherently have " GM-1 binding activity" and thus capable of modulating GM-1 associated activity (using the language of the instant invention) because:

a) GM-1 is located in mucosa and is a binding receptor on mucosal cells. See e.g., Kaper et al (Nature, 1984, 308, 655-658), abstract; therefore, mucosal binding molecules will inevitably bind, at least to some extent, to GM-1;

b) the binding affinity of GM-1 to the mucosa-binding molecules is evidenced by the fact that GM-1 in the referenced method is selected as a linker to bind to mucosa-binding molecules (see claims 13-15).

c) Mucosa-binding molecules of Holmgren, such as B subunit of cholera toxin or enterotoxin, are well known in the art to bind to GM-1. See, e.g, Francis, Kaper et al., abstracts.

Therefore, the prior art composition comprising immunological tolerance-inducing agents anticipates the instantly claimed composition comprising agent capable of modulating GM-1 associated activity.

In regard to claims 11,12, reciting intended use, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. *In re Pearson*, 494 F.2d 1399, 181 USPQ 641 (CCPA 1974). Suggested use limitations do not impart patentability to composition claims where the composition is otherwise anticipated by the prior art.

Conclusion.

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 24, 2003

MICHAEL BORIN, PH.D
PRIMARY EXAMINER